

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Amar Lulla, et al. §
Serial No.: 10/518,016 § Group Art Unit: 1616
Filed: July 6, 2005 § Examiner: Kristie Latrice Brooks
For: COMBINATION OF AZELASTINE AND § Confirmation No.: 4912
STEROIDS §

DECLARATION UNDER 37 CFR § 1.132

I, Geena Malhotra, hereby declare and say that:

1. I am a co-inventor of the invention claimed in the above-identified patent application.
2. Attached as Exhibit A is comparison data for five compositions:

Column 1: Azelastine.HCl

Column 2: Budesonide

Column 3: Azelastine.HCl & Budesonide

Column 4: Fluticasone Propionate

Column 5: Azelastine.HCl and Fluticasone Propionate

Table I of Exhibit A sets forth the ingredient list for the five compositions. Table II of Exhibit A sets forth comparative stability data for the five compositions. The results in Table II show the impurity levels in the initial compositions, and after storage under certain conditions: for example "25/60 RH at 1 M" means the composition was stored for one month at a temperature of 25 degrees C and at a relative humidity of 60. The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone

propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

3. Attached as Exhibit B is a compilation of statements from 6 medical practitioners, labeled B1-B6, along with typed transcriptions. As is self-evident, these statements attest to various advantages and superior results associated with patient use of the DUONASE product comprising azelastine and fluticasone.

4. A pharmaceutical formulation comprising azelastine and fluticasone is commercially available where approved as DUONASE nasal spray, as shown in attached Exhibit C containing information from the following website:

<http://www.cipladoc.com/therapeutic/admin.php?mode=prod&action=disp&id=213>.

5. I am unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid.

6. The present application is licensed to Meda Pharmaceuticals.

7. I, Geena Malhotra, further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: 3rd July 2009,

Geena Malhotra

Name: GEENA MALHOTRA

Exhibit A

Exhibit A, Table I: Comparative Composition data of Azelastine with steroids

Ingredients	Azelastin (% w/w)	Budesonide (% w/w)	Azelastine+B udesonide (% w/w)	Fluticasone (% w/w)	Aze+Flu (% w/w)
Drugs	137 mcg	64 mcg	137+64 mcg	50 mcg	140+50 mcg
MCC+CMC (Avicel RC)	-	-	2.0	0.75	2.0
HPMC	0.10	-	-	-	-
Dispersible cellulose	-	1.25	-	-	-
Dextrose Anhy.	-	-	-	2.5	-
Anhy. Glucose	-	5.0	-	-	-
Glycerin	-	-	2.3	-	2.3
Polysorbate 80	-	0.016	0.005	0.0025	0.005
BKC 10% w/v	0.125	-	0.005	100 ml	0.10
solution					
Phenyl ethyl alcohol	-	-	-	0.125	0.25
Pot sorbate	-	0.12	-	-	-
Disodium EDTA	0.05	0.01	0.01	-	0.01
Sodium Chloride	0.68	-	-	-	-
Citrate	0.048	-	-	-	-
Monohydrate	-	-	-	-	-
Disodium Phosphate	0.322	-	-	-	-
Hydrochloric acid	-	q.s.	-	-	-

Exhibit A

Exhibit A, Table II: Comparative Stability data of Azelastine with steroid Compositions

Stability tests →	Azelastine	Budesonide	Azelastine + Budesonide	Fluticasone	Azelastine + Fluticasone
	INITIAL	INITIAL	INITIAL	INITIAL	INITIAL
Assay	100	97.6	98+97	101.6	100+101.12
pH	6.78	4.51	6.0	6.4	6.1
Total Impurity	0.03	0.26	2.32+0.11	0.52	0.6
	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M
pH	6.86	4.68	5.94	Not Done	Not Done
Total Impurity	0.12	0.25	0.97 + 0.07	Not Done	Not Done
	25/60 RH at 3 M	25/60 RH at 3 M	25/60 RH at 3 M	25/60 RH at 3 M	30/65 RH at 1M
pH	6.76	4.6	5.96	6.21	5.85
Total Impurity	0.13	0.42	5.39+0.16	0.46	0.84
	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M
pH	6.86	4.69	5.92	6.35	5.82
Total Impurity	0.13	0.29	5.53+0.05	0.52	0.89
	40/75 RH at 3 M	40/75 RH at 3 M	40/75 RH at 3 M	40/75 RH at 3 M	40/75 RH at 3 M
pH	6.76	4.61	5.91	5.98	5.81
Total Impurity	0.18	0.49	18.29+0.23	0.53	0.85

Exhibit B1

Dr. C.M. Mathew Chooracken

B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.
Senior Specialist in E.N.T.
Civil Surgeon
District Hospital, Kottayam
Reg. No. 9473

Consultation:
Behind Margin Free Market
Near Kottayam East Police Station
Collectorate P.O., Kottayam - 686 002
Ph: 2564884, Mb: 9447288822

To Cepha Respiratory +

I have been using
the Deconase nasal spray
regularly for my nasal allergies
patients. I found it is
very effective when compared
to the available other nasal
sprays. Oral medications
can be avoided as well.



Kottayam
23/8/05-

Dr. C. M. Mathew Chooracken
B. Sc., M. B. B. S., M.S. (E. N. T.) D. L. O.
Senior Specialist in E. N. T.
Civil Surgeon,
District Hospital, Kottayam
Reg. No. 9473

Dr. C.M.MATHEW CHOORACKEN

To Cipla Respiratory

I have been using the Duonase nasal spray regularly for my nasal allergic patients. I found it is very effective when compared the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Confidential

डॉ. पी. एन. तेजनकर
एम. एस. (ई.एन.टी.)
बाबक, काल, गला एवं शर्दन रोग विशेषज्ञ
पूर्व रजिस्ट्रार ई.एन.टी. हॉस्पिटल, बाब्के

गुजराती समाज, नई सड़क, उज्जैन	जाय मेडिकल सेन्टर (वसावहा ऐड्रेल पम्प के पांच घंटाघर, फ़ियोन, उज्जैन) अंग 251484
मो. 2561981	समय प्राप्त: 11 से 2.00 रात्रिवार अवकाश समय साथ 6 से 8.30

विशेषज्ञ

- नाक एवं साक्ख स्कोर्पी (दूरदीन छारा आपरेशन) • माइक्रोलैरिज्जवल सर्जरी
- माइक्रोइयर सर्जरी (जर्मनी, प्रांत एवं स्वीटजरलेण्ड दो प्रधिकाण प्राप्त) • नाक की प्लारिटक सर्जरी (राइबोफ्लार्टी)

18.8.200

Regarding Dexamethasone

- Using this product - for how many days?
- This is ideal, first line agent for the patient. The combination is adequate to deal with all types of allergy.
- Act on both phases (early and late phase of allergy ie inhibit)
 - inhibiting IL-1 receptor activity & few side effect
 - Act on multi-pheno type allergies
 - The systemic bioavailability is less so can be used for a longer period without side effects.

*Tough to allergy Ref. to HCO**8/2*

DR.P.N.TEJANKAR

CLINIC

M.S. (E.N.T)	Jai Medical Centre (Near
E.N.T and Neck Specialist	Vasavda petrol pump)
Ex-Registrar E.N.T. Hospital, Bombay	Ghantaghlar, Freegunj, Ujjain
	2514884
■ 2561981	Time eve. 6 to 8.30
Time Mor: 11 to 2.00	SUNDAY HOLIDAY

Specialist.....

- Nose and sinus endoscopy • Microlaryngeal Surgery • Microear Surgery (Trained from Germany, France and Switzerland) • Plastic Surgery of the Nose (rhinoplasty)

Regarding Duonase

Using this product for last so many days. This is ideal, first line agent for the patient. The combination is adequate to deal with all type of allergy.

- Acts on both phases (early as well as late phase of allergy i.e. inhibit)
- Antagonises the H1 receptor activity with few side effect.
- Acts on multiple symptoms.
- The systemic bioavailability is less so can be used for a longer period without side effect.

Tough to allergy safe to Nose

Confidential

संग्रहालय अधिकारी, जबलपुर एम.एस.डी.एल.टी.

रजि. नं. ०७९१८८२

कृष्णा जनरल हॉस्पिटल

गल्हायां शेखड़ीगां, ग्रो. सी. एम ती. चौधरी, थोरारी,

पुणे ४११०३२, फँसी ४११५१६

देख: संभाष. १०० टे ८-०० का.

(कैम्प-१०१-वसा)

धन्यवारी कान, नाक, घरा हॉस्पि-

टोल रोड, नायनगं

ता, जुन्ना, सि. पुणे, ४११०

५०१०३२-(हॉस्पि.) ३४४७६६, (फँसी) २३२

रविवार बंद

Date. २७.८.०५

I have prescribed "bunazole Nasal Spray" for 258 patients since Aug 2004 to Aug 2005. And I found that
 @ bunazole Nasal Spray very very effective in all types of allergic rhinitis. Especially in "seasonal allergic rhinitis." Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both in "bunazole Nasal Spray."

So I hereby strongly recommend
 Bunazole Nasal Spray for allergic rhinitis.

DR. PRASAD JAWALEKAR M.S (E.N.T)

Reg.no.071882

E.N.T Specialist

Krishna General Hospital

Dhanvantari E.N.T.Hospital

Gavhane building, P.C.M.T Chowk,

Khodad Road, Narayangaon,

Bhosari,Pune 411039. ☎ 27129516

Taluka Junnar, Dist. Pune 410504

Time: eve. 5-00 to 8-00

SUNDAY CLOSED ☎ 02132-(Hosp.)244766 (R)243969

I have prescribed "Duonase Nasal spray" for 258 patients since Aug 2004 to Aug 2005. And I found that Duonase Nasal Spray very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "Duonase Nasal Spray".

So I hereby strongly recommend Duonase Nasal Spray for allergic rhinitis.

Confidential

No: 25409

Dr. Manish Munjal.M.B.B.S., M.S. Diplomate of National Board (ENT); M.N.A.M.S.
D.H.A., D.N.D., D.N.A., D.T.M., D.M.S.

EAR - NOSE - THROAT AND HEAD-NECK SURGEON

Consultant Otorhinolaryngology & Head-Neck Services
Dayanand Medical College & Hospital, Ludhiana
Formerly Consultant Christian Medical College
and Brown Hospital, Ludhiana.Ph.: 2300182
Mobile : 98551-23462
E-mail : munjal@gilde.net.inClinic-cum-Residence
52-C, Udhian Singh Nagar,
Adj. P.A.U. Gate No.4,
Next to Lions Bhawan, Ludhiana.

Dr.

Pt.

Pr.

Lo.

Rm.

Web.

Csp.

St.

N. Singh
J. S. Singh
B. K. Dabhi

I have been using nasal spray from
the year 1993, ever since I joined my
present institution. I have used beclometasone
dipropionate, budesonide, Azelastine, fluticasone,
mometasone, with other anti-histaminics.
down the line till date.

The present combination spray of a weak
(non-sedating component) Azelastine and
fluticasone (steroidal component) is comp.
by itself in my patients of chronic
sinusitis following nasal sinus
polypsis surgery. Those unwilling
for surgery or unfit for surgery.
There is no response noted within a week
in a few patients but the maximum

time taken: morning 8.00 P.M. to 9.00 P.M. & 5.30 P.M. to 6.30 P.M.
Morning 7.00 am onwards: evening 7.30 to 8.00 P.M.

Confidential

Number of patients respond very well after Three weeks of Therapy.

Recurrences of Polynosis after functional endoscopic sinus surgery is markedly reduced. Eye Itching, Crusting and nasal bleed associated with certain preparations is not noted to that much extent of course caution / avoidance in diabetics and hyperensive patients is required for fear of worsening or inducing fungal pathology. (Rough have not found much literature on this issue on the net)

The combination therapy (Dexoxo) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of the results.

I hoping the future is bright for the combination and no one disagrees. Some contraindication or side effects

DR. MANISH MUNJAL

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used Beclomethasone, Budesonide, Azelastine, Fluticasone, Mometasone, with oral antihistamines down the line till date.

The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroid component) is complete by itself in my patients of chronic simple rhinitis following nasal + sinus polyposis surgery and those unwilling for surgery or unfit for surgery.

There is a response noted within a week in a few patients but the maximum number of patients respond very well after three weeks of therapy.

Recurrences of polyposis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleed as noted with earlier preparations is not noted to that much extent of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening or inducing and fungal pathology (though have not found much literature on the issue on the net).

The combination Therapy (DUONASE) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of results.

Hoping the future is bright for this combination and no one digs up some contra indication or side effect of this indication.

Exhibit B5

VATS E.N.T. CENTRE

(दिल्ली सरकार हारा पंजीकृत)

698/5, Yamuna Vihar Road, (Road No. 58), Maujpur, Delhi-110053

: 229111
Ph. : 229164
: 229111
Dr. Suresh Vats

M.B.B.S., D.M.S. (ENT)
CONSULTANT EAR, NOSE & THROAT SURGEON
Formerly ENT Surgeon
ST. STEPHEN'S HOSPITAL
LNJP & GB PANT HOSPITAL

डॉ सुरेश वट्स

एम.बी.बी.एस., डॉ.एन्टी.एन्टी.

कान, नाक व गला दोनों विभागों एवं सर्जन

समय: सुबह 10 से 1 बजे शाम 6 से 8 बजे

Reimbursable Yes/No. S. No. (प्रदाता अम्बाल)

Name Age & Sex Resl. Date A/

Name:

रामेश यों नेक्ट Audiometry एवं Speech Therapy
उम्र: ३५. वृक्ष पुरा 10 से 1 व ऊपर वाय 7 से 8 वर्षों

P.T. Audiogrammatic Assessment

Nidit Audiogram

Hearing Aid Trial

Speech Assessment

Speech Therapy

Cleft Lip

Impediment

Hb TLC, B.I.C, S.T., G.T.

ESR, Mt-Tu

Blood Sugar R.F.R.P., Blood Urea

Urine R.P. & Micro

Prothrombin time Platelets Count

HbA1c, HbV I & II

ACE I/E, Nasal smear for Aspergillus

VDRL, ABO Type

T3 T4 TSH

Cytomegalovirus for AFB

Cytomegalovirus/Varicella C & B

Blood - BSL & OBT

PNAC

X-Ray Mandible - Lateral, Oblique(ER) Towne

X-Ray PNS - Waters

X-Ray Naso-Thyroid soft tissue (Lateral)

X-Ray Neck soft Tissue - Lateral

X-Ray cervical Spine - Lat. & AP

X-Ray - Epiphyses Patelloe (Post-Lateral)

X-Ray Occluded view for of mouth

X-Ray - Submandibular region, Post, Lat. & L

X-Ray - Internal Auditory Meatus

X-Ray - TMJ, Joint Lat. Open & closed jaw

X-Ray - Nasal Bones - Lateral

X-Ray - Skull - AP - Lateral

X-Ray - Chest PA, View

Barium swallow

C.T. Scan - PNS - Coronal 3 mm cuts

C.T. Scan - Temporal bones

C.T. Scan - Neck - Head

ECG

R . L

Rinne's
Weber's

I/L Exa.:



Right Left



No. 698/5 Yamuna Vihar Road, New Delhi-110053

*Disease nasal flora
is unique & distinct from
the available nasal flora
due to it- Combined full
allergic & anti-inflammatory
property. It is an oral
product, effective in the
patients of Allergic
Rhinitis with or w/o
concomitant bronchitis*

Allerg: Wrote Trynes say
to use in certain patients w/
oral antihistamine may be harm

17/8/08
Dr. SUKESHB VATS
Sr. CONSULTANT M.S. (ENT)
THROAT SURGEON, NOSE &
Rep. No. MCI. 2108, DMC 1112
698/S, Rohi Nu 5th Mainjewi, Delhi-53

Dr. SURESH VATS

Duonase Nasal spray is unique & distinct from other available nasal sprays due to its combined Anti-allergic & anti-inflammatory properties. It is an excellent product, effective in majority of patients with allergic Rhinitis with or without concomitant Bronchial Allergy. Worth Trying. Safe to use in certain patients where oral antihistamine may be harmful.

Exhibit B6

डॉ. बी. बी. माथुर
एम.डी.

मिस्ट विशेषज्ञ एवं एसोसिएट प्रोफेसर
चोट एवं टी.बी. विभाग
सरकारी पटेल मेडिकल कॉलेज, बीकानेर
RMC No. 7458

Dr. B. B. Mathur
M.D.

Senior Consultant & Associate Professor
Chest & T.B., Hospital
S.P. Medical College, BIKANER
O Hos. :0151-2226333, Res. 0151-2528789

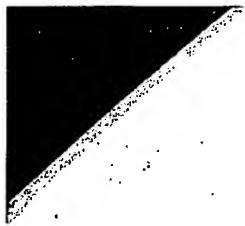
Ref No.

Date... 17/8/05

Duohaze Nasal Spray is highly effective
in controlling symptoms and subsequent relapse.
I have used this product in many patients and find
it effective as it gives confidence to patients &
its take care symptoms due to rapid onset &
anti-inflammatory action giving relief due to anti-

inflammatory action

Dr. B. B. Mathur
एसोसिएट प्रोफेसर
सी. सी. एंड डीस्ट विभाग
पटेल मेडिकल कॉलेज
बीकानेर (राज.)



Dr. B.B. MATHUR

Duonase Nasal spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients as it takes care of symptoms due to rapid onset of action and long lasting relief due to anti-inflammatory action.



Cipla

Therapeutic Index

Nasal Preparations

Duonase Nasal Spray

Azelastine hydrochloride & Fluticasone propionate

Each spray delivers

Azelastine hydrochloride BP 140 mcg

Fluticasone propionate BP 50 mcg

Composition

Fluticasone propionate BP 0.0357% w/v

Azelastine Hydrochloride BP 0.10% w/v

Benzalkonium Chloride NF 0.01% w/v

(as preservative)

Phenyl Ethyl alcohol USP 0.25% v/v

(as preservative)

Description

Duonase is an antihistamine-corticosteroid combination available as a metered spray formulation for intranasal administration. It contains azelastine hydrochloride, which is a second generation H 1 receptor antagonist with potent topical activity and fluticasone propionate, synthetic corticosteroid with anti-inflammatory properties.

Pharmacology

As Duonase is a combination of Azelastine and Fluticasone; the pharmacological properties of both the molecules are given separately.

Pharmacology of Azelastine Hydrochloride

Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H 1-receptor antagonism in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H 1-receptor antagonist activity.

Pharmacokinetics and Metabolism

After intranasal administration, the systemic bioavailability of azelastine hydrochloride is approximately 40%. Maximum plasma concentrations (C_{max}) are achieved in 2-3 hours. Following intravenous and oral administration, the elimination half-life, steady-state volume of distribution, and plasma clearance are 22 hours, 14.5 L/kg, and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine. Azelastine is oxidatively metabolized to a principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. Specific P450 isoforms responsible for the biotransformation of azelastine have not been identified; however, clinical interaction studies with the known CYP3A4 inhibitor erythromycin failed to demonstrate a pharmacokinetic interaction. In a multiple-dose, steady-state drug interaction study in normal volunteers, cimetidine (400 mg twice daily), a nonspecific P450 inhibitor, raised orally administered mean azelastine (4 mg twice daily) concentrations by approximately 65%.

The major active metabolite, desmethylazelastine, was not measurable (below assay limit) following single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing of azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine reached

from 20-50% of azelastine concentrations. When azelastine hydrochloride is administered desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranasal route.

Pharmacology of Fluticasone Propionate

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory and immunomodulatory properties.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to natural hormone. However, the clinical significance of these findings in relation to the low levels is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Pharmacokinetics:

Absorption: Fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (0.01 ng/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral doses of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg .

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcartin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, $1,090 \text{ mL/min}$), with renal clearance accounting for less than 0.02% of the total. The only circulatory metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had a low affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human hepatocytes in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of the radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Indications

Duonase is indicated for the management of symptoms of allergic rhinitis once the need for antihistamine and corticosteroid has been established. It is recommended to treat **moderate to severe persistent symptoms** in adults above 12 years. For children above 5 years **Duonase** is recommended for **severe symptoms** of allergic rhinitis. **Duonase** can be used for treating non-allergic vasomotor rhinitis in adults and children 12 years of age and older.

Dosage And Method of Administration

Adults and children 5 years and older: 1 spray/nostril twice daily

The recommended dosage should not be exceeded. Not recommended for use in children under 5 years.

Contraindications

Duonase is contraindicated in patients with or known hypersensitivity to azelastine hydrochloride or fluticasone propionate or any of the components of the preparation.

Warnings and Precautions

- Concurrent use of this combination with alcohol or other CNS depressants or other antihistamines should be avoided as additional reductions in alertness and additional impairment of CNS performance may occur due to azelastine.
- The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. Some patients may experience symptoms of withdrawal e.g. joint and/or muscular pain, lassitude and depression.
- The concomitant use of an intranasal corticosteroid with other corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis. Therefore the combination should be used cautiously in patients with other pathological conditions requiring steroids.
- Intranasal corticosteroids may cause a reduction in growth velocity when administered at higher dose. The recommended dosage of **Duonase** should not be exceeded.
- Special care is needed in patients with lung tuberculosis and fungal and viral infections. Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles for example can have a more serious and potentially fatal course in children on immunosuppressant corticosteroids.
- During long term therapy, monitoring of hematological and adrenal function is advised.
- In clinical studies with intranasal fluticasone propionate, the development of localized infections of the nose and the pharynx with *Candida albicans* has been seen rarely. If such an infection develops, it may require treatment with appropriate local therapy and discontinuation of the treatment with **Duonase** is advised.

Drug Interactions

The use of **Duonase** in patients taking concurrent drugs, which are potent inhibitors of the cytochrome 450 3A4 system eg. Ketoconazole and protease inhibitors such as ritonavir may be associated with increased systemic exposure of fluticasone.

Pregnancy

The combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether azelastine hydrochloride or fluticasone propionate is excreted in human milk. Hence, caution should be exercised while prescribing this combination to nursing mothers.

Undesirable Effects

The most likely side effects with this combination are headache, somnolence, pharyngitis, epistaxis, nasal burning/irritation, nausea, vomiting, cough, taste disturbance. The combination may produce a bitter taste, which may lead to occasional nausea. Bitter taste disappears sometime.

Shelf Life

2 years

Storage and Handling Instructions

Store below 30 °C.

Do not refrigerate.

Protect from direct sunlight.

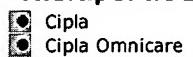
Packaging Information**Duonase Nasal Spray**

Sales pack contains 70 metered doses

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